TEMPORAL TRENDS IN ADOPTION AND OUTCOMES OF TRANSCATHETER AORTIC VALVE IMPLANTATION: A SWISSTAVI REGISTRY ANALYSIS.

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ABSTRACT

Aims: To describe temporal trends in adoption and performance of transcatheter aortic valve implantation (TAVI) in Switzerland over a period of 5 years.

Methods and Results: Between 2011 and 2015, a total of 3'493 patients were consecutively included in the SwissTAVI Registry (NCT01368250) and analyzed for the purpose of this study. The primary outcome measure was all-cause mortality at 1-year after TAVI. Over the five-year period, a six-fold increase in the number of procedures was observed, whereas the baseline surgical risk estimated by the Society of Thoracic Surgeon (STS) score declined (from 6.8 ± 4.4% to 4.6 ± 3.6, $p<0.001$). Overall, 1-year mortality amounted to 12.8%; mortality was highest in the first annual cohorts (14.6%, 14.8% and 15.9% in 2011, 2012 and 2013, respectively) and decreased to 13.4% in 2014 and 9.7% in 2015, with a significant temporal trend. While rates of cerebrovascular events, peri-procedural myocardial infarction, moderate/severe paravalvular regurgitation and stage 3 acute kidney injury did not significantly change over time, a significant reduction in life threatening or major bleeding was noted during the latest compared with earlier years of recruitment.

Conclusions: This long-term recruitment analysis of a national TAVI registry showed rapid adoption paralleled by a progressive decrease of patients' baseline risk profile. Early and late survival significantly improved over time as did the rate of life threatening or major bleeding.

Key words: *aortic stenosis, transcatheter aortic valve implantation, mortality, trends*

INTRODUCTION

During the past 15 years, transcatheter aortic valve implantation (TAVI) has transformed the treatment of patients with symptomatic, severe aortic stenosis and assumed a Class I recommendation for use in patients at increased surgical risk.[1] TAVI has demonstrated superiority over conservative therapy in inoperable patients [2] and non-inferiority or superiority compared with surgical aortic valve replacement in patients at high or intermediate operative risk.[3-6] As for other innovative procedures, randomized trials and observational studies provide complementary evidence to support the expansion of TAVI.[7] Specifically, the contribution of nationwide registries is key to assess patterns of changing patient characteristics, procedural features and clinical outcomes in routine clinical practice.[8-12] In addition, comprehensive recording of procedures within national registries is essential for a comparative evaluation of the quality of care of heart valve centers as well as for setting new performance goals.[1]

The SwissTAVI Registry (NCT01368250) is a national, prospective registry initiated by the Swiss Working Group of Interventional Cardiology in collaboration with the Swiss Society of Cardiac Surgery with the aim to assess the safety and effectiveness of consecutive TAVI procedures performed in Switzerland since 2011. In-hospital and 30-day clinical outcomes of patients included between February 2011 and March 2013 have been previously presented.[13] This report describes temporal trends in TAVI volume and performance during a 5-year period and reports on the primary outcome measure of major adverse cardiac and cerebrovascular events since the initiation of the registry over time.

METHODS

Design and setting

The SwissTAVI Registry is performed under the lead of the Swiss Cardiovascular Center Bern at Bern University Hospital and is based on the collection of clinical, procedural and follow-up data of consecutively included patients undergoing TAVI at 14 sites (**Supplemental Table S1**). A

multidisciplinary heart team is responsible for the decision to perform TAVI at each participating site. The use of CE-approved devices is mandatory while the type of access route is left to operators' discretion. The SwissTAVI Registry aims to assess the rates of major adverse cardiac and cerebrovascular events at one-year (primary outcome).

Data collection

A web-based database (www.swisstavi.ch) with standardized case-report forms is used for anonymized data collection at baseline and during follow-up that is performed through scheduled clinical visits or phone interviews at 30-days and annually after the procedure. Clinical events occurring during the procedure or follow-up are blinded for patient details and the performing center and are adjudicated following review of original source documents by a dedicated clinical event committee. The SwissTAVI Clinical Event Committee consists of interventional cardiologists and cardiac surgeons and events are assessed and adjudicated according to the updated criteria of the Valve Academic Research Consortium (VARC-2).[14] The Clinical Trials Unit Bern is responsible for central data monitoring to verify completeness and accuracy of data and independent statistical analysis. The study protocol was approved by the local cantonal ethic committee at each site and all patients provided written informed consent before inclusion.

Study endpoints

The primary study endpoint of the present analysis is all-cause mortality 1-year after the procedure. Secondary endpoints include cardiovascular mortality, cerebrovascular accident, myocardial infarction, stage 3 acute kidney injury (AKI), life threatening or major bleeding, vascular access site complications, structural valve deterioration and repeat unplanned intervention. In addition, standardized mortality ratios (SMRs) were calculated to compare trends in mortality of TAVI patients compared with an age- and gender-matched general population during the respective year of treatment (downloaded from Bundesamt für Statistik, Switzerland)**.**[15]

Statistical analysis

Continuous and categorical variables are reported as mean ± standard deviation and as number and percentage, respectively. 30-day event rates are reported using time-to-first-event data, graphically presented using Kaplan-Meier curves, with incidence rates calculated from life tables. Baseline patient clinical characteristics and procedural feature by calendar year were compared using ANOVA, Kruskall-Wallis or Chi-square tests (categorical variables). Event rates at 30 days and 1 year were compared through the 5-year period (2011-2016) using Weibull regressions with a shared frailty by hospital (14 sites). Reported are crude hazard ratio (HR, with 95% confidence intervals, CI) and p-value testing for an overall linear trend over the 5-year period from Weibull regression, or overall difference from Fisher's exact test in case of zero events. Reported are adjusted hazard ratios ($HR_{adj,}$ with 95% confidence intervals, CI) for comparisons including adjustment for the STS-PROM (Society of Thoracic Surgeons-Predicted Risk Of Mortality) score and type of access route. Adjusted p-values testing for an overall linear trend over the five periods.

SMR is an epidemiologic measure that describes the impact disease has on the likelihood of death compared with the general population. The indirect SMRs (adjusted for age and sex) (with exact 95% confidence intervals [95% CIs]) in the three study cohorts, as compared to the general population, were determined by calculating the ratio of the observed mortality rate to the expected mortality rate within the same period of time, using the method described by Ulm.[15] Observed deaths referred to the actual number of deaths of patients. Expected deaths referred to the number of deaths expected from the population statistics within the same period (year), stratified by sex and age. The age- and sex-specific mortality rates in the general population were obtained from the Swiss Bundesamt für Statistik matched on year of procedure. All analyses were performed using Stata (version 14.2; StataCorp LP, College Station, TX). Statistical significance was determined by a 2-sided $p<0.05$.

RESULTS

Demographic and clinical patient characteristics

From February 15, 2011 to February 15, 2016, 3'493 consecutive patients were prospectively included in the SwissTAVI Registry. Annual procedural rates increased approximately linearly from 208 in 2011 to 1'254 in 2015. At the same time the STS-PROM score gradually decreased (from 6.8 ± 4.4% in 2011 to 4.6 ± 3.6% in 2015, p<0.001). While a numerical increase of the STS PROM was observed between 2011 and 2013 (p=0.64), the significant decrease during the overall observational period was mainly related to the last 2 years of patient inclusion. (**Figure 1**). **Table 1** shows baseline characteristics over time. Mean age of the overall population was 82.1 ± 6.4 years and remained stable during the years. There were also no significant differences in sex, diabetes mellitus, coronary artery disease, previous cardiac surgery and left ventricular ejection fraction. However, patients that underwent TAVI in the latest compared with earlier years of recruitment had less often chronic obstructive pulmonary disease as well as New York Heart Association (NYHA) functional class III or IV.

Procedural characteristics

As reported in **Table 2**, trends in the use of different CE-approved transcatheter heart valves changed over time. Overall, the Medtronic self-expanding (CoreValve and Evolut R, Medtronic, Minneapolis, Minnesota) and the Edwards balloon-expandable (Sapien THV/XT and Sapien 3, Edwards Lifesciences, Irvine, California) transcatheter heart valves were most commonly used. The proportion of patients undergoing balloon aortic valvuloplasty during the index procedure before valve implantation decreased from 93.8% in 2011 to 54.9% in 2015 (p<0.001).

The use of the transfemoral access progressively increased up to 92.1% of procedures performed in 2015; consistently, rates of procedures performed by means of other access routes, including transapical, trans-subclavian and direct aortic, declined over time (**Figure 2**). Concomitant coronary revascularization was less frequently performed in the latest compared with earlier years of recruitment.

A significant decrease in procedural time and total amount of contrast volume was observed over time. Overall, rates of procedural complications requiring conversion to surgery remained very low over the years. Mean length of index hospitalization significantly decreased from 2011 to 2015.

Clinical outcomes

Overall, all-cause mortality was observed at a rate of 3.8% at 30-day follow-up. It was highest in 2011 (5.8%) and steadily decreased to 4.6% in 2012, 4.9% in 2013, 4.0% in 2014 and 2.5% in 2015, with a significant temporal trend (p= 0.02). **Figure 3** shows rates of observed and expected mortality, as calculated by the STS-PROM scoring system. Cardiac mortality decreased by half over the years (HR_{adj} 0.86, 95% CI 0.75-0.99, p= 0.034).

Rates of primary and secondary study endpoints are reported in **Table 3**. **Figure 4** shows rates of events occurring within 30-days after TAVI for each year of recruitment: cerebrovascular events, myocardial infarction, and moderate/severe paravalvular regurgitation did not significantly change over time. Life threatening or major bleeding events occurred less frequently in the latest compared with earlier years of recruitment (HR_{adj} 0.92, 95% CI 0.85-0.99, p= 0.033). Overall, permanent pacemaker implantation was needed in 18.6% of patients: while rates of pacemaker implantation after TAVI with balloon-expandable devices were stable over the time (**Table 3**), a progressive reduction was observed in patients treated with self-expanding devices (**Supplemental Table S2**). The decrease of rates of stage 3 AKI across years was not significant in adjusted analysis.

All-cause mortality at one year occurred in 12.8% of patients and was highest in 2011 (14.6%), 2012 (14.8%) and 2013 (15.9%) and decreased to 13.4% in 2014 and 9.7% in 2015, with a significant temporal trend (p<0.001). Similarly, the overall rate of cardiac mortality was higher in 2011 (10.4%), 2012 (10.9%) and 2013 (11.0%) and decreased to 9.9% in 2014 and 6.1% in 2015, with a significant temporal trend also after adjustment for confounders (HR_{adj} 0.90, 95C% CI 0.82-0.99, p= 0.033). Kaplan-Meier curves of all-cause and cardiac mortality at 1-year are shown in **Figure 5A** and **B**. Rates of cerebrovascular events, myocardial infarction, structural valve deterioration and repeat unplanned valvular interventions were comparable across the years.

Mortality after TAVI compared with the general population in Switzerland

In the overall TAVI patient population, SMRs were found to be four-fold higher throughout the observational period and were highest among male patients when compared with an age- and gender matched general population in Switzerland. However, we observed a statistical trend towards a reduction of SMRs as shown in **Figure 6.** Specifically, the SMRs of the entire cohort were 3.81 (95% CI 2.66-5.45) in 2011, 4.56 (95% CI 3.61-5.76) in 2012, 5.03 (95% CI 4.11-6.16) in 2013, 4.96 (95% CI 4.16-5.91) in 2014 and 3.75 (95% CI 3.13-4349) in 2015. Among males, the SMRs were 3.83 (95% CI 2.27-6.46) in 2011, 5.08 (95% CI 3.73-6.93) in 2012, 5.52 (95% CI 4.18-7.29) in 2013, 6.02 (95% Ci 4.79-7.58) in 2014 and 4.97 (95% CI 3.96-6.23) in 2015. Similarly, the SMRs for female patients were 3.79 (95% CI 2.32-6.19) in 2011, 3.97 (95% CI 2.78-5.68) in 2012, 4.59 (95% CI 3.42-6.17) in 2013, 3.97 (95% CI 3.03-5.21) in 2014 and 2.62 (95% CI 1.95—3.54) in 2015.

DISCUSSION

The salient findings of our study investigating temporal trends in adoption and performance of TAVI in Switzerland can be summarized as follows:

- TAVI was rapidly adopted in Switzerland with an annual increase in procedure rates and a significant decrease in the estimated risk profile
- The use of transapical and other alternative access routes progressively declined in favor of the transfemoral access
- We observed a relevant decrease in procedural duration and length of index hospitalization over time
- Life threatening or major bleeding declined over the years, whereas rates of other procedure-related complications remained stable
- All-cause and cardiac mortality were significantly lower in the latest compared with earlier years of patient treatment

- Overall, patients undergoing TAVI had a four-fold increased risk of mortality compared with an age- and gender-matched general population

The observed increase of annual TAVI procedures is in line with the global trend of TAVI dissemination with a projected more than four-fold increase in volume over the next 10 years.[7] Population ageing, increased awareness of the disease and robust evidence of clinical benefit of the procedure in a broad spectrum of patients with severe aortic stenosis are the major drivers of this expansion.

Along the same line, the tendency to treat lower risk patients is consistent with other registries: a steep decrease in the logistic EuroSCORE was reported between patients included in the FRANCE 2 and FRANCE TAVI in 2010-2012 and 2013-2015, respectively;[16] an increasing proportion of intermediate/low-risk patients over time was observed in the German TAVI registry;[10] among 26,414 patients in the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry, a significant decline of the STS-PROM occurred from 2012-2013 to 2014.[8] A multitude of reasons may explain this common trend that occurred prior to the results of randomized trials in lower risk patients were made available.[5, 6] First of all, accumulating evidence of favorable clinical and hemodynamic results of TAVI from observational studies may have favored its adoption in lower risk patients.[17, 18] In addition, factors other than the classical surgical risk scores are increasingly considered by multidisciplinary heart teams for the choice between TAVI and surgery (frailty, geriatric assessment). In this context, it is important to note that the mean age amounted to 82 years and did not significantly decrease despite a decrease in STS risk scores.[19] The tendency to treat elderly but lower risk patients is influenced by the evidence provided from the pivotal TAVI trials: in the randomized comparisons with surgery, high- and intermediate-risk cohorts were defined on the basis of the mean STS score, whereas the mean age of included patients continued to reflect an elderly population (over 80 years of age). [19] Ongoing studies investigating clinical outcomes after TAVI in low-risk patients will focus for the first time on the comparative performance also in younger patients. There is no age restriction for the inclusion in the PARTNER 3 (NCT02675114) and in the Medtronic

Low risk trial (NCT02701283) and also NOTION-2 includes patients at the age of 75 or younger (NCT02825134). A change in clinical practice is expected on the basis of the results of these studies.

Furthermore, different policies for reimbursement of TAVI procedures may influence the evolution of patients' characteristics over time across different countries. In the United Kingdom, only minimal changes in the baseline profile of patients treated from 2007 and 2012 were observed, probably as consequence of a position statement from regulators of health care that restricted the funding to patients with Logistic EuroSCORE >20 and STS-PROM score >10.[20] Overall, increasing procedure volume and changing features of patients receiving TAVI concur to ameliorate clinical outcomes. Similarly, in the TVT Registry, an association between procedure volume and risk-adjusted outcomes was reported from 2011 to 2015, with early mortality, vascular complications and bleeding events significantly declining from the first to the 400th case.[21] Finally, the STS score undergoes regular updates and calculation of the risk score today differs from calculations performed several years ago.

Transfemoral TAVI has emerged as the preferred strategy over the 5-year period and rates of transfemoral TAVI procedures progressively increased over time. The reason for this increase is most likely reflected by the ongoing development of TAVI devices. The availability of innovative devices featuring lower profiles of delivery systems contribute to enlarge the proportion of patients whose anatomic features are suitable for transfemoral procedures. This trend was observed in previous reports,[8, 10] and may have influenced clinical outcomes in successive years. Cumulative evidence from randomized trials showed a significant survival advantage of TAVI performed through transfemoral rather than other access routes over conventional surgery.[22] Similarly, the reduction in procedure duration and length of hospitalization may be attributed to technological improvement, growing operator experience and the lower operative risk of patients.

Although site-reported, all clinical events recorded in the SwissTAVI Registry are adjudicated based on clinical source documents by a clinical event committee consisting of cardiologists and surgeons. This represents one of the major strengths with respect to other registries. In this context, it is reassuring that rates of the most debilitating peri-procedural adverse events such as cerebrovascular events and

myocardial infarction remained low over time. In particular, 30-day rates of stroke during the most recent years (1.7% in 2014 and 2015) represent the lowest rate reported so far, within randomized and observational studies. The lack of a further reduction of cardiac and cerebrovascular ischemic event rates over time, despite a more favorable risk profile of patients, can be explained by the fact that procedure- rather than patient-related factors may have a greater impact on the occurrence of such events. In this perspective, the use of a transfemoral access first strategy and preventive coronary revascularization in patients with significant disease of proximal segments of main coronary vessels may have ensured the lowest rates of stroke and myocardial infarction, so far. Stage 3 AKI also declined throughout the study period, probably as result of procedural advances (reduction of contrast volume, lower use of balloon valvuloplasty) and more favorable profile of patients at baseline. Although the trend was not significant after adjustment for confounders, low occurrence of post-procedural renal dysfunction may have a positive impact on clinical outcomes, given the well-known association of advanced acute renal injury with higher risk of mortality and re-hospitalization.[23, 24] Similarly, the observed significant reduction of early life-threatening or major bleeding events may have contributed to ameliorate 30-day survival over time.

In the entire population, moderate/severe paravalvular regurgitation and the need for PPM after TAVI occurred in 5.6% and 18.6% of patients, respectively, without significant changes during the following years. These are actually considered the current main limitations of TAVI compared with surgery and might be related to certain devices features. It should be noted that our observations are limited at years between 2011 and 2015 while the most frequent generation of devices (Edwards Sapien 3, Medtronic Evolut R) were only introduced in 2014. However, although the frequency of these events is well within the range of other reported TAVI series,[16, 20] a further decline in rates is warranted. Several lines of evidence support the association between more than mild residual paravalvular regurgitation and an increased risk of mortality, also in intermediate risk patients.[5] In addition, although there is conflicting evidence on the impact of PPM implantation on survival, sustained loss of

atrioventricular synchrony by chronic pacing may affect cardiac function at longer term, especially in younger patients.[25]

Rates of 30-day and 1-year mortality (3.8% and 12.8%, respectively) in the overall population were significantly lower than those observed in other registries[8, 20] but compare favorably with the results of recent randomized trials such as the PARTNER 2A (3.9% and 12.3%, respectively).[5] The low rates of mortality in 2015 (2.5% at 30-day and 9.7% at 1-year) provide reassurance about the safety and efficacy of the procedure among lower risk patients and set a benchmark that should inform the decision process of local heart teams and patient counselling.

Limitations

The results of the present study should be interpreted taking into account the following limitations. The description of temporal trends and associations does not provide evidence of causality. Moreover, we were not able to assess the impact of the learning curve of operators across centers participating into the registry on clinical outcomes after TAVI. Finally, as adverse event reporting is left to the discretion of each site, a certain underreporting of events and bias cannot be excluded.

Conclusions

This long-term recruitment analysis of a national TAVI registry showed rapid adoption paralleled by a progressive decrease of patients' baseline risk profile. Early and late survival significantly improved over time as did the rate of life threatening or major bleeding.

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Figure Legends

Figure 1. Cumulative TAVI procedures and STS-PROM score of patients included in the SwissTAVI Registry from 2011 to 2015.

Since the initiation of the registry in 2011, there was a rapid expansion of annual rates of procedures paralleled by a progressive change in baseline risk profile of patients.

STS-PROM, The Society of Thoracic Surgeons- Predicted Risk Of Mortality; TAVI, Transcatheter aortic valve implantation.

Figure 2. Temporal trends of access routes for TAVI.

Progressive increase of transfemoral approach (blue line) and parallel decrease of use of other access routes (including transcapical, direct aortic and trans-subclavian, red line) for TAVI.

TAVI, Transcatheter aortic valve implantation.

Figure 3. Observed and expected rates of mortality (STS PROM) (upper panel**); Ratio of observed vs. expected rates of mortality (**lower panel**) by year of inclusion in the SwissTAVI Registry.**

Figure 4. Rates of procedure-related and other early adverse event across study years.

From 2011 to 2015, rates of stroke, myocardial infarction, stage 3 acute kidney injury, and moderate/severe paravalvular regurgitation did not significantly change over the time. Rates of life-threatening or major bleeding significantly decreased in subsequent years. AKI, Acute Kidney Injury; PVL, Paravalvular leak.

Figure 5. Mortality at 1-year in patients included in the SwissTAVI Registry between 2011 and 2015.

Kaplan-Meier curves of all-cause (A) and cardiac (B) mortality at 1-year after TAVI according to the year of inclusion in the registry.

Figure 6. SMRs of TAVI patients.

Age- and sex-adjusted standardized mortality ratios (SMRs) of TAVI patients (overall population and stratified by gender). Results are shown as the SMR with 95% confidence intervals.

Table Legends

Table 1. Baseline characteristics per year of inclusion

Table 2. Procedural characteristics per year of inclusion

Table 3. Clinical outcomes at 30-day and 1-year after TAVI per year of inclusion

Table 1

TABLE 1. Baseline characteristics per year of inclusion

	All years N = 3493	2011 N = 208	2012 N = 474	2013 N = 596	2014 N = 961	2015 N = 1254	p-value
Age (years)	82.1±6.4	82.4±5.6	82.3±6.3	82.3±6.4	82.1±6.5	82.0±6.6	0.80
Female gender, n(%)	1733 (49.6%)	112 (53.8%)	245 (51.7%)	287 (48.2%)	469 (48.8%)	620 (49.4%)	0.54
Body mass index (kg/m^2)	26.6±5.1	26.5±5.1	26.2±4.8	26.6±5.0	26.8± 5.2	26.6±5.2	0.33
Diabetes mellitus, n(%)	885 (25.3%)	61 (29.3%)	136 (28.7%)	144 (24.2%)	238 (24.8%)	306 (24.4%)	0.21
Previous PPM, n (%)	359 (10.3%)	18 (8.7%)	48 (10.1%)	61 (10.2%)	98 (10.2%)	134 (10.7%)	0.93
Previous MI, n (%)	496 (14.2%)	30 (14.4%)	74 (15.6%)	93 (15.6%)	135 (14.0%)	164 (13.1%)	0.54
Previous cardiac surgery, n (%)	527 (15.1%)	26 (12.5%)	75 (15.8%)	93 (15.6%)	147 (15.3%)	186 (14.8%)	0.82
Previous CVA, n(%)	396 (11.3%)	28 (13.5%)	55 (11.6%)	63 (10.6%)	107 (11.1%)	143 (11.4%)	0.85
Peripheral vascular disease, n (%)	599 (17.2%)	38 (18.3%)	90 (19.0%)	101 (16.9%)	166 (17.3%)	204 (16.3%)	0.73
Chronic obstructive pulmonary disease, n (%)	445 (12.7%)	33 (15.9%)	76 (16.0%)	84 (14.1%)	125 (13.0%)	127 (10.1%)	0.004
Coronary artery disease, n (%)	2013 (57.6%)	118 (56.7%)	265 (55.9%)	360 (60.4%)	566 (58.9%)	704 (56.1%)	0.36
LVEF, (%)	54.8±14.1	54.7±13.5	54.1±14.1	53.9±14.3	55.4±14.0	55.2±14.3	0.27
Aortic valve area, cm^2	0.71 ± 0.24	0.71 ± 0.22	0.72 ± 0.24	0.70 ± 0.26	0.70 ± 0.22	0.71 ± 0.25	0.54
Mean gradient, mmHg	44.1±19.1	43.6±18.2	44.4±17.0	43.0±18.2	46.2±21.5	43.1±18.6	0.006
Moderate/severe mitral regurgitation, n (%)	669 (20.4%)	39 (20.5%)	86 (19.8%)	126 (22.5%)	171 (18.8%)	247 (21.0%)	0.51
Symptoms							
NYHA I or II, n(%)	1165 (34.1%)	41 (19.9%)	139 (29.3%)	205 (34.5%)	309 (33.5%)	471 (38.7%)	<0.001
NYHA III or IV, n(%)	2250 (65.9%)	165 (80.1%)	335 (70.7%)	390 (65.5%)	613 (66.5%)	747 (61.3%)	<0.001
No Angina, n(%)	2696 (77.4%)	138 (67.0%)	330 (69.6%)	497 (83.4%)	746 (78.0%)	985 (78.9%)	<0.001
CCS I or II, n(%)	514 (14.8%)	34 (16.5%)	90 (19.0%)	59 (9.9%)	137 (14.3%)	194 (15.5%)	0.001
CCS III or IV, n(%)	271 (7.8%)	34 (16.5%)	54 (11.4%)	40 (6.7%)	73 (7.6%)	70 (5.6%)	<0.001
Logistic EuroScore (%)	19.4±13.8	20.9±11.9	20.2±12.9	22.4±16.0	19.4±13.9	17.5±13.1	<0.001
STS-PROM Score (%)	5.8±4.4	6.8±4.4	7.1±4.7	7.3±5.4.1	5.7± 4.2	4.6±3.6	<0.001

CCS, Canadian Cardiovascular Society; CVA, Cerebrovascular accident; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PPM, Permanent pacemaker; STS-PROM, The Society of Thoracic Surgeons- Predicted Risk Of Mortality.

Table 2

TABLE 2. Procedural characteristics per year of inclusion

	All years	2011	2012	2013	2014	2015	p-value
	N = 3493	N = 208	N = 474	N = 596	N = 961	N = 1254	
Device implanted							<0.001
Medtronic CoreValve, n(%)	914 (26.2%)	97 (46.6%)	229 (48.3%)	282 (47.3%)	231 (24.0%)	75 (6.0%)	<0.001
Edwards Sapien XT, n(%)	606 (17.3%)	104 (50.0%)	206 (43.5%)	265 (44.5%)	27 (2.8%)	4 (0.3%)	<0.001
Symetis Acurate, n(%)	98 (2.8%)	0 (0.0%)	16 (3.4%)	19 (3.2%)	19 (2.0%)	44 (3.5%)	0.021
JenaValve, n(%)	57 (1.6%)	6 (2.9%)	18 (3.8%)	17 (2.9%)	12 (1.2%)	4 (0.3%)	<0.001
SJM Portico, n(%)	87 (2.5%)	0 (0.0%)	1 (0.2%)	4 (0.7%)	18 (1.9%)	64 (5.1%)	<0.001
Medtronic Engager, n(%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0.045
Direct Flow Medical, n(%)	34 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (1.6%)	19 (1.5%)	0.001
Edwards Sapien 3, n(%)	1164 (33.3%)	0 (0.0%)	0 (0.0%)	5 (0.8%)	566 (58.9%)	593 (47.3%)	<0.001
BSC Lotus, n(%)	186 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	58 (6.0%)	128 (10.2%)	<0.001
Medtronic Evolut R, n(%)	334 (9.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (1.5%)	320 (25.5%)	<0.001
No device*, n(%)	11 (0.3%)	1 (0.5%)	4 (0.8%)	2 (0.3%)	1 (0.1%)	3 (0.2%)	0.19
Access routes							<0.001
Femoral, n(%)	3047 (87.2%)	167 (80.3%)	372 (78.5%)	507 (85.1%)	846 (88.0%)	1155 (92.1%)	<0.001
Transapical, n(%)	357 (10.2%)	39 (18.8%)	85 (17.9%)	70 (11.7%)	88 (9.2%)	75 (6.0%)	<0.001
Subclavian, n(%)	34 (1.0%)	2 (1.0%)	5 (1.1%)	7 (1.2%)	11 (1.1%)	9 (0.7%)	0.84
Direct aortic, n(%)	34 (1.0%)	0 (0.0%)	12 (2.5%)	8 (1.3%)	10 (1.0%)	4 (0.3%)	<0.001
Other, n(%)	21 (0.6%)	0 (0.0%)	0 (0.0%)	4 (0.7%)	6 (0.6%)	11 (0.9%)	0.21
Procedure location							<0.001
Catheterization laboratory, n(%)	1554 (44.5%)	48 (23.1%)	198 (41.8%)	388 (65.1%)	391 (40.7%)	529 (42.2%)	<0.001
Operating room, n(%)	40 (1.1%)	1 (0.5%)	7 (1.5%)	13 (2.2%)	14 (1.5%)	5 (0.4%)	0.008
Hybrid room, n(%)	1899 (54.4%)	159 (76.4%)	269 (56.8%)	195 (32.7%)	556 (57.9%)	720 (57.4%)	<0.001
Procedural details							
General anaesthesia, n(%)	1502 (43.0%)	78 (37.5%)	295 (62.4%)	249 (41.8%)	402 (41.8%)	478 (38.1%)	<0.001
Balloon Aortic Valvuloplasty, n(%)	2536 (72.6%)	195 (93.8%)	394 (83.1%)	498 (83.6%)	760 (79.1%)	689 (54.9%)	<0.001
Concomitant procedures							
Percutaneous coronary intervention, n(%)	237 (6.8%)	31 (14.9%)	34 (7.2%)	47 (7.9%)	58 (6.1%)	67 (5.3%)	<0.001
In- hospital course							
Any PRBC Infusion, n(%)	540 (15.5%)	30 (14.4%)	102 (21.5%)	106 (17.8%)	128 (13.3%)	174 (13.9%)	<0.001
Overall In-Hospital Stay (days)	10.1±6.0	11.3±7.3	10.5±5.7	10.4±6.3	9.9±6.0	9.7±5.9	0.002

*Procedure aborted before device was implanted. PPM, Permanent Pacemaker; PRBC, Packed Red Blood Cells.

Table 3

TABLE 3. Clinical outcomes at 30-day and 1-year after TAVI per year of inclusion

	All years	2011	2012	2013	2014	2015	Linear trend Hazard Ratio (95% CI)	p-value	Adj. Linear trend Hazard Ratio (95% CI)	Adj. Linear trend p-value
	N =3493	N = 208	N = 474	N = 596	N = 961	N =1254				
At 30-day										
Mortality	132 (3.8)	12 (5.8)	22 (4.6)	29 (4.9)	38 (4.0)	31 (2.5)	0.82 (0.72-0.93)	0.002	0.89 (0.77-1.02)	0.08
Cardiac Mortality	122 (3.5)	12 (5.8)	22 (4.6)	25 (4.2)	36 (3.8)	27 (2.2)	0.80 (0.70-0.91)	0.001	0.86 (0.75-0.99)	0.034
Cerebrovascular Accident	130 (3.8)	7 (3.4)	18 (3.8)	24 (4.1)	33 (3.5)	48 (3.8)	1.01 (0.88-1.16)	0.92	1.03 (0.89-1.19)	0.70
Disabling Stroke	69 (2.0)	5 (2.4)	14 (3.0)	13 (2.2)	16 (1.7)	21 (1.7)	0.86 (0.71-1.03)	0.092	0.88 (0.73-1.06)	0.18
Non-Disabling Stroke	48 (1.4)	1 (0.5)	3 (0.7)	9 (1.5)	13 (1.4)	22 (1.8)	1.29 (0.99-1.67)	0.057	1.32 (1.01-1.72)	0.044
TIA	13 (0.4)	1 (0.5)	1 (0.2)	2 (0.3)	4 (0.4)	5 (0.4)	1.09 (0.69-1.72)	0.72	1.07 (0.67-1.72)	0.76
Myocardial Infarction	22 (0.6)	1 (0.5)	3 (0.6)	3 (0.5)	9 (0.9)	6 (0.5)	1.02 (0.72-1.44)	0.90	1.05 (0.73-1.50)	0.79
Peri-procedural	19 (0.5)	0 (0.0)	3 (0.6)	3 (0.5)	7 (0.7)	6 (0.5)	1.11 (0.76-1.61)	0.60	1.16 (0.78-1.72)	0.46
Spontaneous	3 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0.65 (0.28-1.50)	0.31		
Acute Kidney Injury	165 (4.8)	24 (11.8)	30 (6.4)	35 (6.0)	38 (4.0)	38 (3.0)	0.79 (0.70-0.89)	<0.001	0.84 (0.74-0.95)	0.005
Stage 1	63 (1.8)	13 (6.4)	13 (2.8)	10 (1.7)	11 (1.2)	16 (1.3)	0.73 (0.61-0.88)	0.001	0.76 (0.62-0.92)	0.005
Stage 2	29 (0.8)	3 (1.5)	6 (1.3)	5 (0.9)	9 (0.9)	6 (0.5)	0.83 (0.63-1.09)	0.18	0.87 (0.65-1.16)	0.33
Stage 3	73 (2.1)	8 (3.9)	11 (2.4)	20 (3.4)	18 (1.9)	16 (1.3)	0.81 (0.67-0.96)	0.018	0.88 (0.73-1.06)	0.17
Bleeding	592 (17.0)	51 (24.7)	92 (19.5)	92 (15.5)	140 (14.6)	217 (17.4)	0.97 (0.91-1.04)	0.45	0.99 (0.92-1.06)	0.69
Life Threatening or major	465 (13.4)	41 (19.8)	81 (17.2)	74 (12.5)	120 (12.5)	149 (11.9)	0.90 (0.84-0.97)	0.007	0.92 (0.85-0.99)	0.033
Minor	133 (3.8)	11 (5.4)	11 (2.4)	19 (3.2)	22 (2.3)	70 (5.6)	1.26 (1.09-1.46)	0.002	1.25 (1.07-1.45)	0.005
Vascular access site complications	548 (15.7)	38 (18.3)	77 (16.3)	100 (16.8)	136 (14.2)	197 (15.7)	1.01 (0.95-1.09)	0.70	1.01 (0.94-1.08)	0.79
Major	337 (9.7)	23 (11.1)	48 (10.1)	57 (9.6)	89 (9.3)	120 (9.6)	1.00 (0.91-1.09)	0.96	1.01 (0.92-1.10)	0.89
Minor	209 (6.0)	15 (7.2)	31 (6.5)	41 (6.9)	43 (4.5)	79 (6.3)	1.03 (0.92-1.15)	0.61	1.01 (0.90-1.13)	0.87
Pacemaker implantation	641 (18.6)	48 (23.6)	89 (19.1)	103 (17.6)	183 (19.3)	218 (17.6)	0.98 (0.91-1.04)	0.46	0.97 (0.90-1.03)	0.30

At 1-year										
Mortality	437 (12.8)	30 (14.6)	70 (14.8)	94 (15.9)	125 (13.4)	118 (9.7)	0.88 (0.82-0.94)	<0.001	0.93 (0.86-1.01)	0.070
Cardiac Mortality	301 (8.9)	21 (10.4)	51 (10.9)	64 (11.0)	92 (9.9)	73 (6.1)	0.85 (0.78-0.93)	<0.001	0.90 (0.82-0.99)	0.033
Cerebrovascular Accident	166 (4.9)	12 (6.1)	20 (4.3)	30 (5.2)	42 (4.5)	62 (5.1)	1.01 (0.89-1.14)	0.93	1.01 (0.89-1.15)	0.84
Disabling Stroke	84 (2.5)	6 (2.9)	15 (3.2)	15 (2.6)	22 (2.4)	26 (2.1)	0.89 (0.76-1.05)	0.17	0.91 (0.76-1.07)	0.25
Non-Disabling Stroke	61 (1.8)	4 (2.2)	3 (0.7)	10 (1.7)	14 (1.5)	30 (2.5)	1.23 (0.98-1.55)	0.071	1.25 (0.99-1.58)	0.063
TIA	21 (0.6)	2 (1.0)	2 (0.5)	5 (0.9)	6 (0.6)	6 (0.5)	0.94 (0.66-1.32)	0.70	0.91 (0.64-1.29)	0.60
Myocardial Infarction	45 (1.4)	4 (2.2)	7 (1.6)	5 (0.9)	17 (1.9)	12 (1.0)	0.93 (0.73-1.17)	0.51	0.95 (0.75-1.21)	0.70
Bleeding	675 (19.6)	56 (27.3)	101 (21.6)	103 (17.6)	173 (18.4)	242 (19.5)	0.99 (0.93-1.05)	0.66	1.00 (0.94-1.06)	0.96
Life threatening or major	527 (15.3)	46 (22.5)	87 (18.5)	80 (13.6)	143 (15.2)	171 (13.8)	0.92 (0.86-0.99)	0.024	0.94 (0.88-1.01)	0.095
Minor	165 (4.9)	12 (5.9)	15 (3.3)	25 (4.4)	36 (4.0)	77 (6.3)	1.22 (1.07-1.39)	0.003	1.20 (1.05-1.37)	0.007
Repeat unplanned intervention	80 (2.4)	3 (1.6)	13 (2.9)	9 (1.6)	23 (2.5)	32 (2.7)	1.09 (0.90-1.31)	0.38	1.06 (0.87-1.28)	0.57
Valve in Valve treatment	16 (0.5)	1 (0.5)	2 (0.4)	5 (0.9)	3 (0.3)	5 (0.4)	0.89 (0.61-1.31)	0.56	0.84 (0.57-1.24)	0.39
Surgical revision	15 (0.4)	0 (0.0)	2 (0.4)	1 (0.2)	5 (0.5)	7 (0.6)	1.34 (0.83-2.16)	0.23	1.12 (0.70-1.80)	0.64
Other intervention	51 (1.6)	2 (1.1)	10 (2.2)	4 (0.7)	15 (1.7)	20 (1.7)	1.06 (0.85-1.33)	0.60	1.06 (0.84-1.34)	0.60
Pacemaker implantation	694 (20.3)	54 (26.8)	98 (21.2)	115 (19.8)	191 (20.3)	236 (19.1)	0.96 (0.90-1.02)	0.23	0.95 (0.90-1.02)	0.15

Figure1

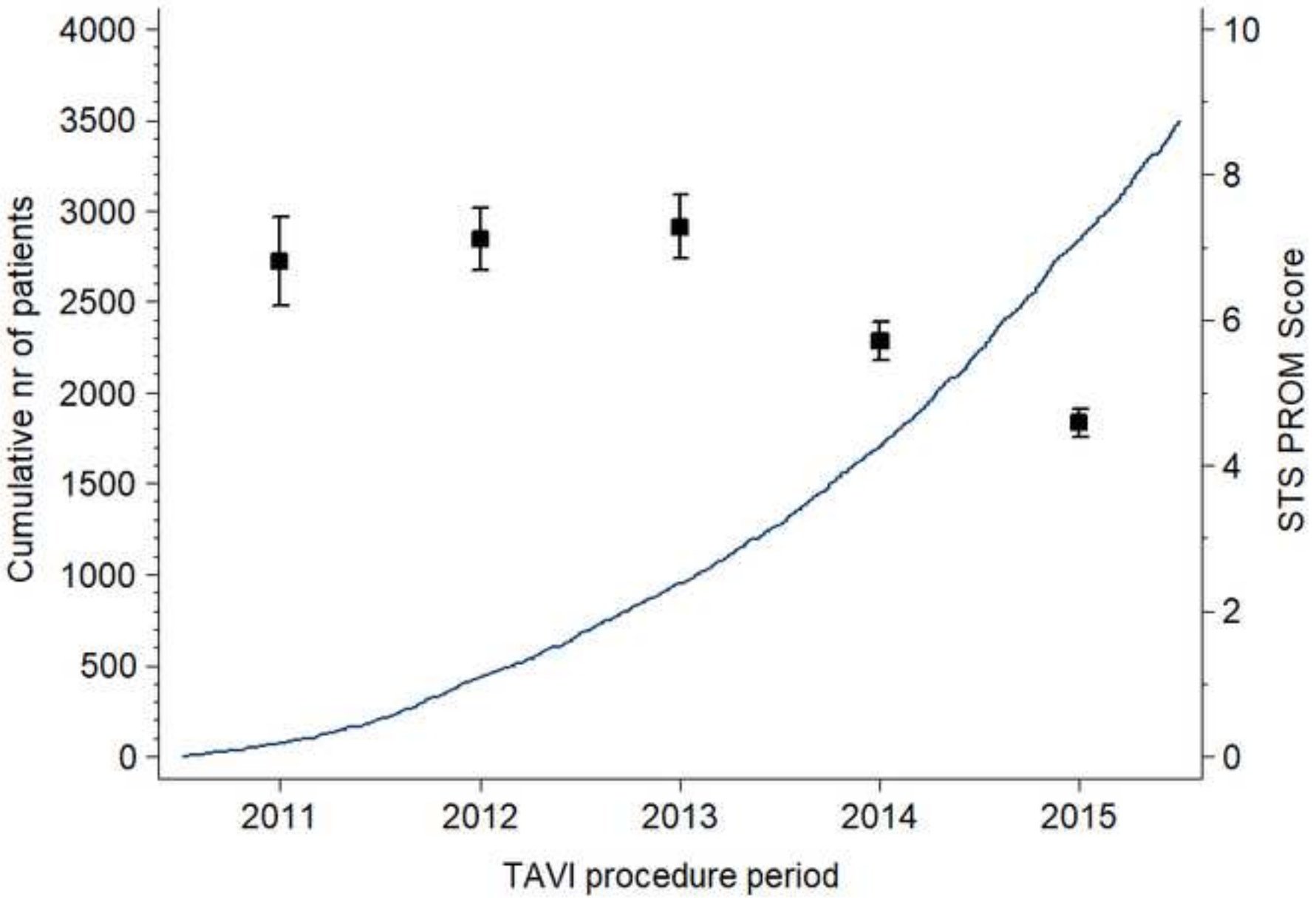

Cumulative nr of patients
4000
3500
3000
2500
2000
1500
1000
500
0
STS PROM Score
10
8
6
4
2
0
2011
2012
2013
2014
2015
TAVI procedure period

Figure2

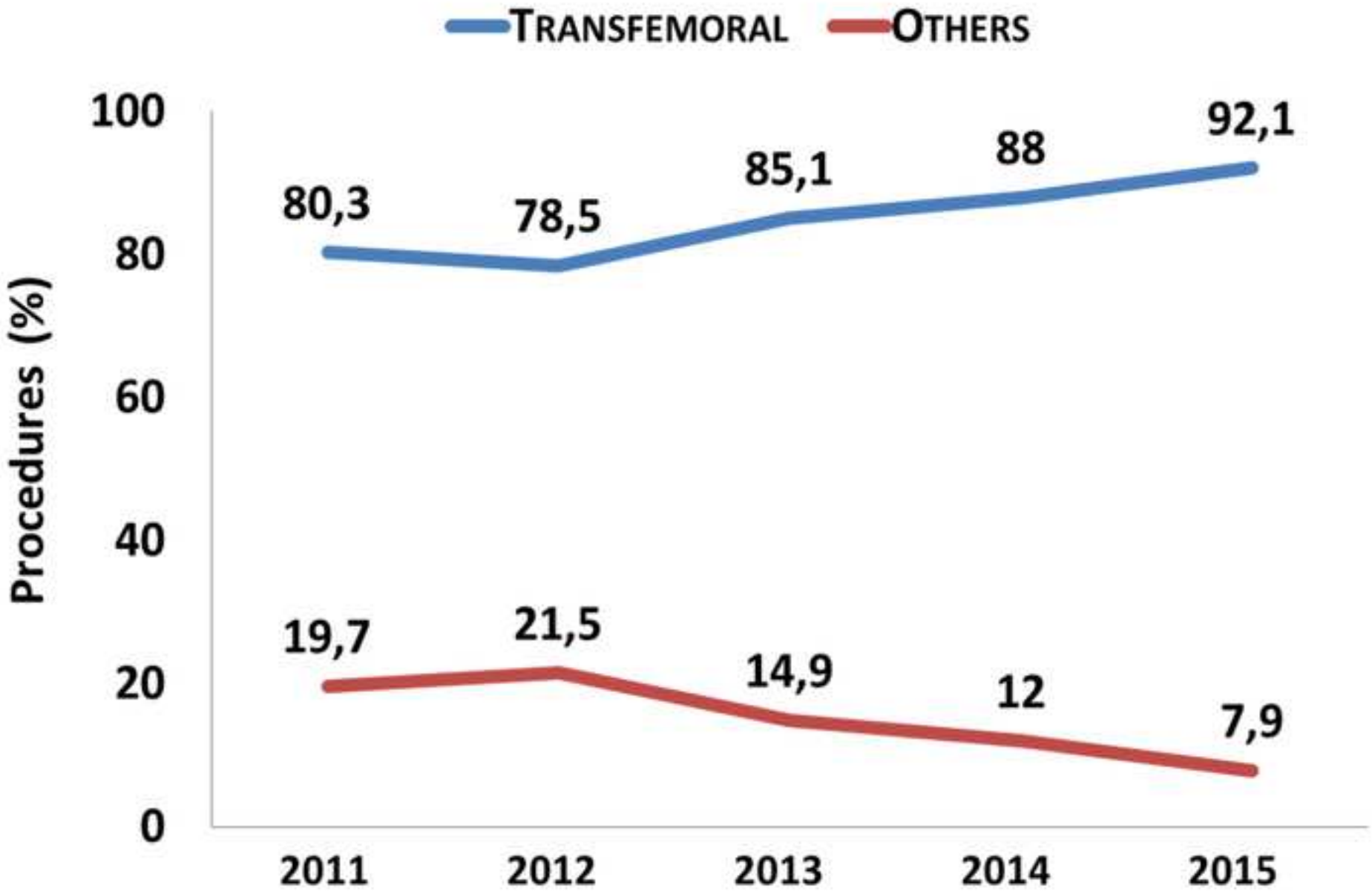
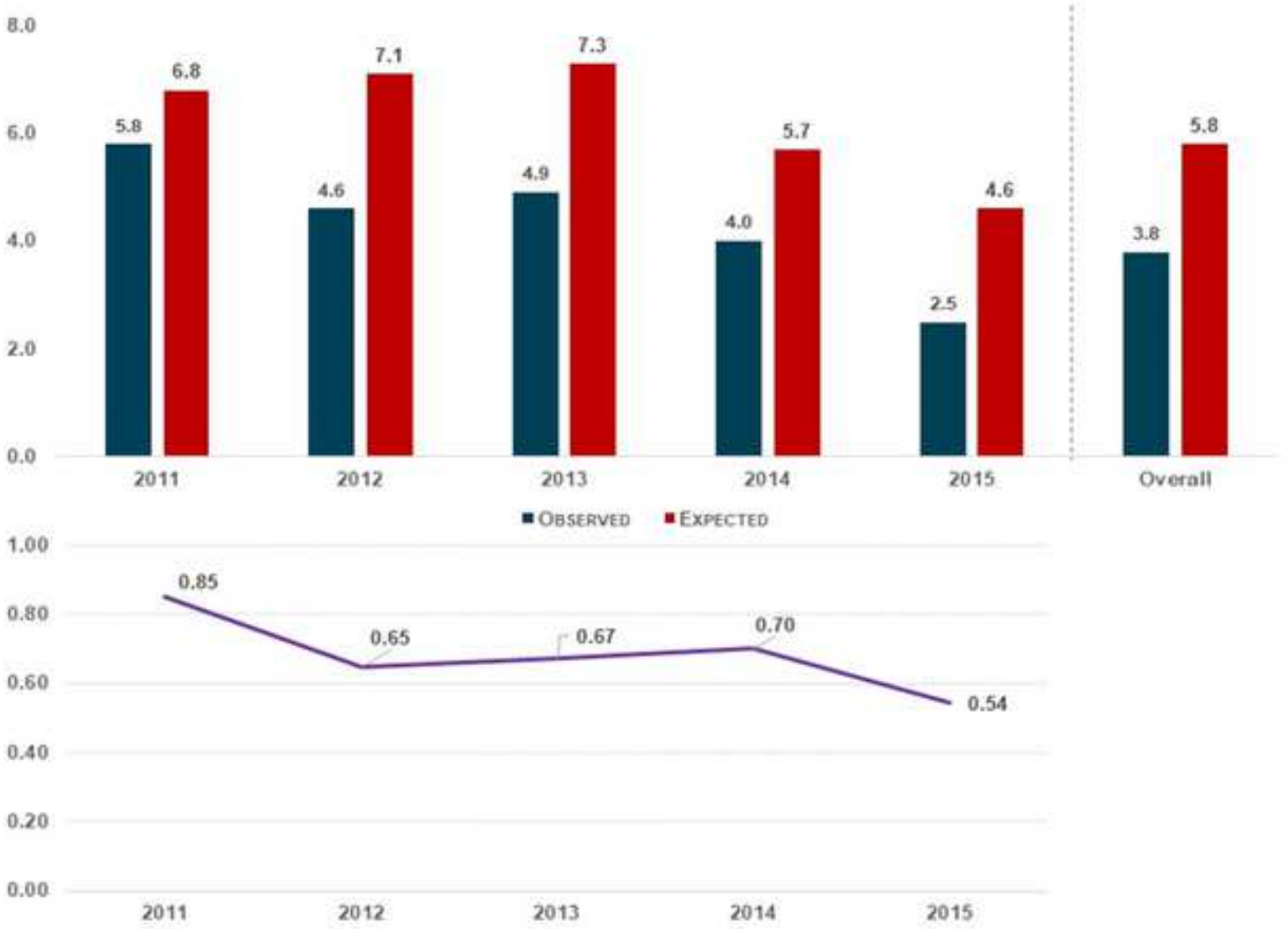

TRANSFEMORAL
OTHERS
Procedures (%)
100
80
60
40
20
0
80,3
78,5
85,1
88
92,1
19,7
21,5
14,9
12
7,9
2011
2012
2013
2014
2015

Figure3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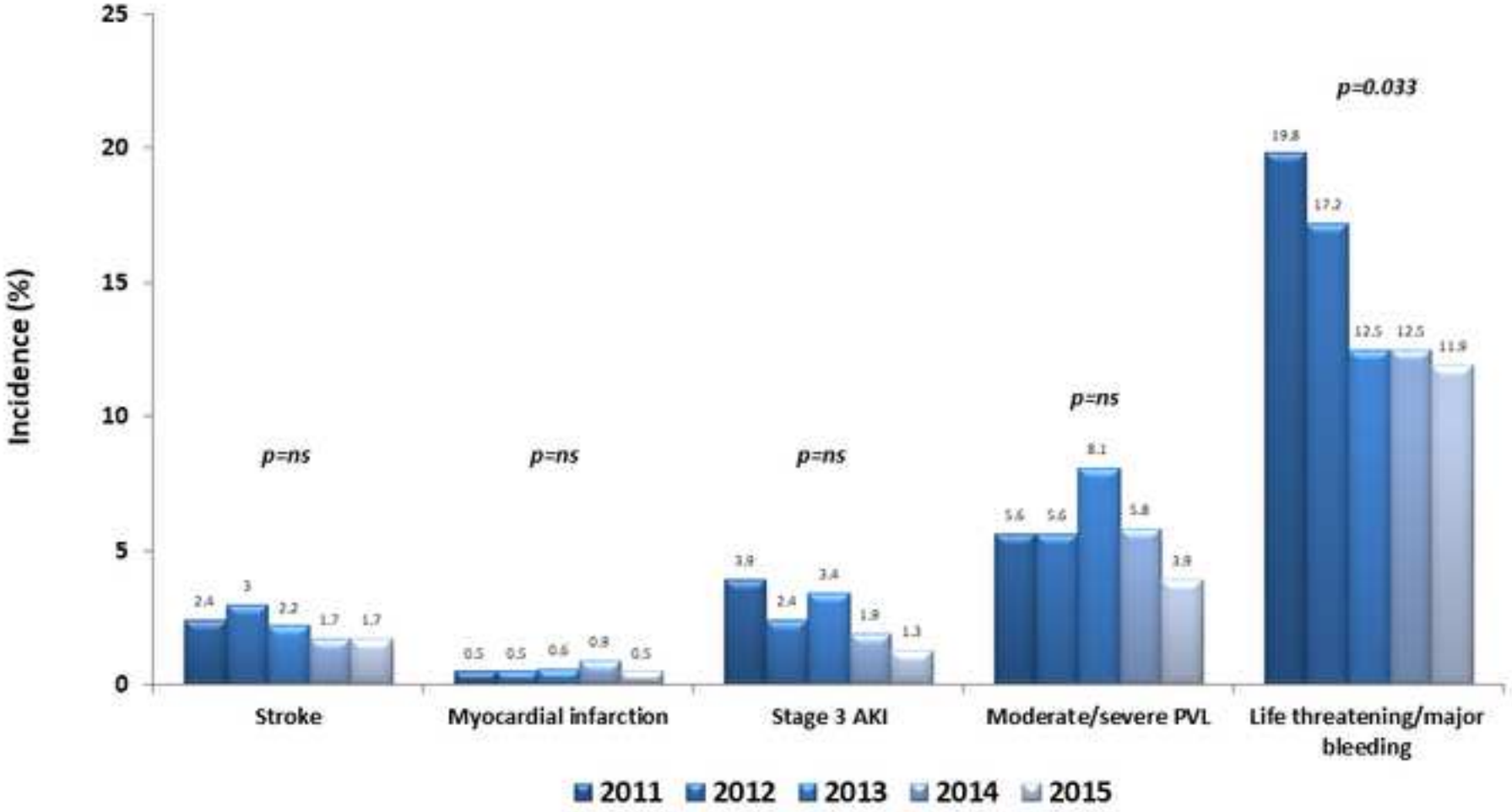
2.0
0.0
5.8
6.8
4.6
7.1
4.9
7.3
4.0
5.7
2.5
4.6
3.8
5.8
2011
2012
2013
2014
2015
Overall
OBSERVED
EXPECTED
1.00
0.80
0.60
0.40
0.20
0.00
0.85
0.65
0.67
0.70
0.54
2011
2012
2013
2014
2015

Figure4


Incidence (%)
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20
15
10
5
0
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p=ns
p=ns
p=ns
p=0.033
2.4
3
2.2
1.7
1.7
0.5
0.5
0.6
0.9
0.5
3.9
2.4
3.4
1.9
1.3
5.6
5.6
8.1
5.8
3.9
19.8
17.2
12.5
12.5
11.9
Stroke
Myocardial infarction
Stage 3 AKI
Moderate/severe PVL
Life threatening/major bleeding
2011
2012
2013
2014
2015

Figure5

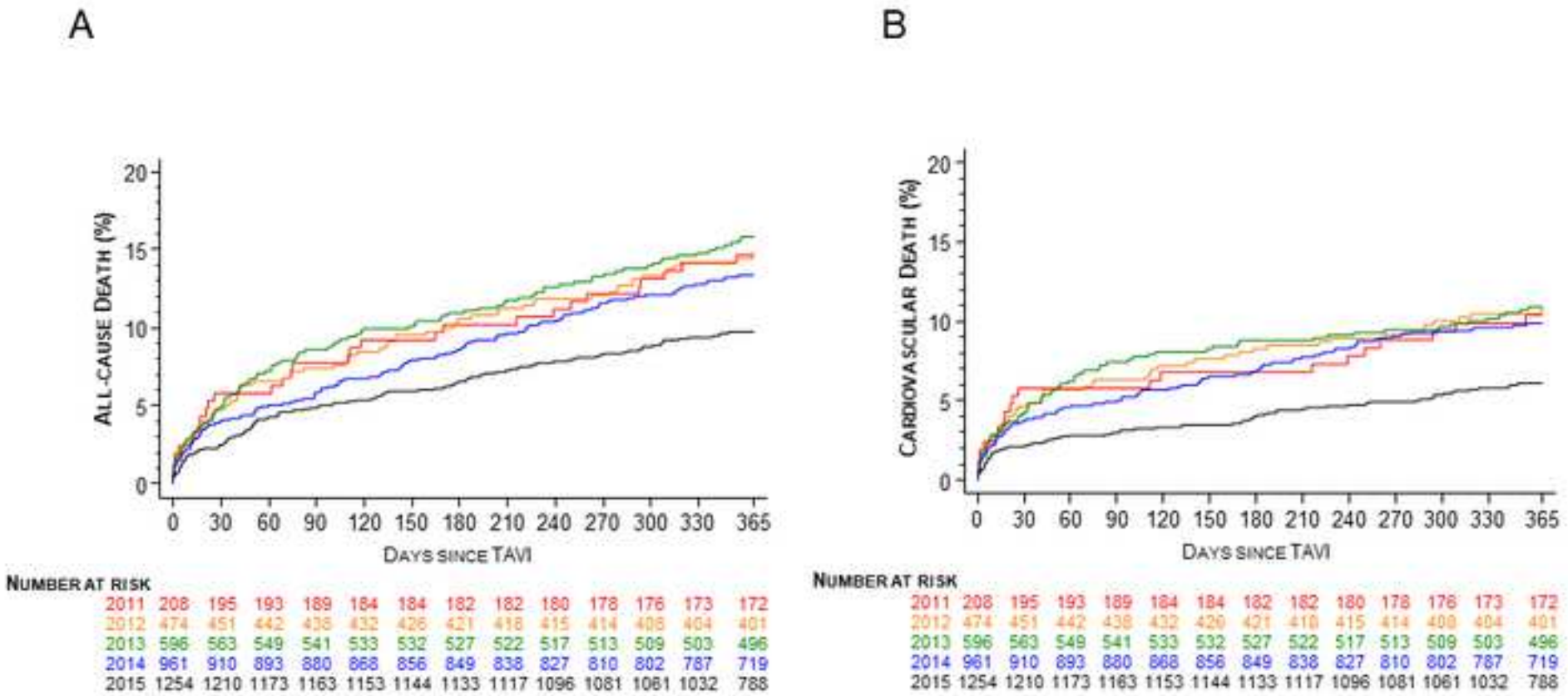
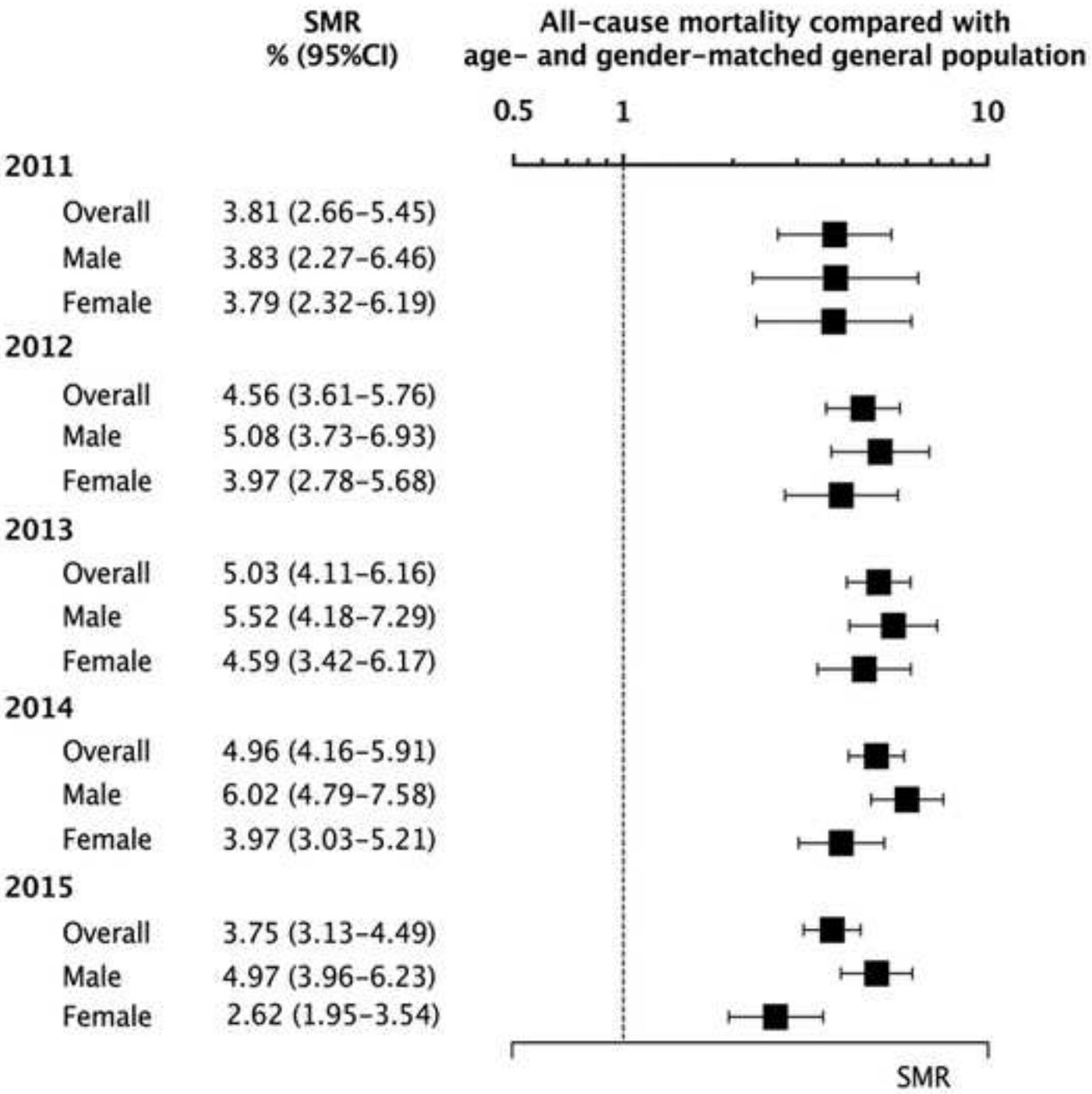

A
ALL-CAUSE DEATH (%)
0
5
10
15
20
0 30 60 90 120 150 180 210 240 270 300 330 365
DAYS SINCE TAVI
NUMBER AT RISK
2011 208 195 193 189 184 184 182 182 180 178 176 173 172
2012 474 451 442 438 432 426 421 418 415 414 408 404 401
2013 596 563 549 541 533 532 527 522 517 513 509 503 496
2014 961 910 893 880 868 856 849 838 827 810 802 787 719
2015 1254 1210 1173 1163 1153 1144 1133 1117 1096 1081 1061 1032 788
B
CARDIOVASCULAR DEATH (%)
0
5
10
15
20
0 30 60 90 120 150 180 210 240 270 300 330 365
DAYS SINCE TAVI
NUMBER AT RISK
2011 208 195 193 189 184 184 182 182 180 178 176 173 172
2012 474 451 442 438 432 426 421 418 415 414 408 404 401
2013 596 563 549 541 533 532 527 522 517 513 509 503 496
2014 961 910 893 880 868 856 849 838 827 810 802 787 719
2015 1254 1210 1173 1163 1153 1144 1133 1117 1096 1081 1061 1032 788

Figure6


SMR
% (95%CI)
All-cause mortality compared with
age- and gender-matched general population
0.5
1
10
2011
Overall 3.81 (2.66-5.45)
Male 3.83 (2.27-6.46)
Female 3.79 (2.32-6.19)
2012
Overall 4.56 (3.61-5.76)
Male 5.08 (3.73-6.93)
Female 3.97 (2.78-5.68)
2013
Overall 5.03 (4.11-6.16)
Male 5.52 (4.18-7.29)
Female 4.59 (3.42-6.17)
2014
Overall 4.96 (4.16-5.91)
Male 6.02 (4.79-7.58)
Female 3.97 (3.03-5.21)
2015
Overall 3.75 (3.13-4.49)
Male 4.97 (3.96-6.23)
Female 2.62 (1.95-3.54)
SMR